Please add the following claims:

41. (new) A peptide which comprises an analogue of the carboxyl-terminal sequence of a growth hormone, said analog comprising the amino acid sequence:

Tyr-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe (SEQ ID NO:19)

wherein all amino acids, except for glycine, are of the L-absolute configuration, unless indicated as D-absolute configuration, and the peptide has a cyclic disulfide bond between Cys(182) and Cys(189) or an organic or inorganic acid addition salt thereof.

42. (New) A peptide according to claim 1, of the sequence:

Tyr-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe (SEQ ID NO:19).

43. (New) A pharmaceutical composition for use in the treatment of obesity in an animal, which comprises an effective amount of a peptide according to claim 41, together with one or more pharmaceutically acceptable carriers and diluents.

44. (New) A pharmaceutical composition for use in the treatment of obesity in an animal, which comprises an effective amount of a peptide according to claim 42, together with one or more pharmaceutically acceptable carriers and diluents.

A marked up copy of the amendments to the claims showing the additions in bold and underline and deletions in bold and brackets is attached hereto.

REMARKS

After entry of this amendment, claims 1, 7-18, 34, 36, and 39-44 will be pending in this application. Claims 37 and 38 have been cancelled. New claims 41-44 have been added. A check covering the cost of the additional claim fees is included herewith. Claims 8-10, 12, 14, 15, 17-18, 34 and 40 have been withdrawn from consideration as drawn to a nonelected invention.

Amendment of the claims is supported by the application as filed, does not add new matter, and is otherwise proper. Applicants respectfully request entry of this amendment in its entirety. In view of the amendment and following remarks, applicants respectfully request reconsideration of the application and claims and submit that the application is in condition for allowance.

1. Drawings

Applicants note that a Notice of Draftsperson's review objecting to various drawings contained in the application was attached to the Office Action was. In response thereto, enclosed are clean, formal copies of the drawings for the draftsperson's consideration. Accordingly, applicants respectfully request the objections to the drawings be withdrawn.

2. Election/Restriction

The Office Action stated that "it would appear claims 8-10, 12, 14, and 15 do not encompass the elected peptide. Therefore, these claims are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention." Applicants respectfully disagree that claims 8-10 and 15 do not encompass the elected peptide. Specifically, claim 8 recites that "positions 182 and 189 are selected from the group consisting of L-Cys, D-Cys..." The elected peptide has a cysteine at positions 182 and 189 and thus claim 8 clearly covers the elected peptide. Claim 9 covers peptides where positions 183 and 186 are joined by a salt bridge between a positively charged amino acid and a negatively charged amino acid and claim 10 recites that the positively charged amino acid can be L-Arg or D-Arg and the negatively charged amino acid can be L-Glu or D-Glu. In the elected peptide, position 183 is an arginine residue and 186 is a glutamic acid residue. Thus, these claims also clearly cover the elected peptide. Claim 15 covers peptides having specific groups at their terminal end. The elected peptide does not exclude such embodiments and therefore is also covered by claim 15. Additionally, applicants respectfully submit that the independent claims from

which claims 8-10, 12, 14, and 15 ultimately depend is allowable. Accordingly, applicants respectfully request the Examiner reconsider the withdrawal of these claims.

3. Priority

The Office Action noted that application did not "contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet." Applicants would like to thank the Examiner for her attention to detail and have amended the first sentence of the specification to include a reference to the applications to which priority is claimed.

4. Double Patenting

Claim 39 was "objected to under 37 CFR 1.75 as being a substantial duplicate of claim 37." Claim 37 has been cancelled rendering the objection moot and respectfully request the Examiner withdraw this objection.

5. Claim Rejections —35 USC §102 (Novelty)

In the Office Action, claims 1, 7, 11, 36, 37 and 39 were "rejected under 35 U.S.C. 102(b) as being anticipated by Wade *et al.* (Acta Endocrinologica 101: 10-14, 1982)." Specifically, the Office Action stated that

> Wade *et al.* disclose a peptide of human growth hormone consisting of amino acids 177-191 of the human growth hormone. Wade *et al.* teach that the protein has a disulfide bond between the cysteine residues at positions 182 and 189... Wade *et al.* do not disclose an amide covalent bond between residues 183 and 186. However, in view of the disulfide bond which is normally formed these amino acids would be in close proximity to one another and owing to their positive and negative charges, the amide bond be inherent to the peptide of Wade *et al.* absent to the contrary.

In order "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." MPEP §2112. Applicants respectfully submit this rejection is improper because it has shifted the burden

to the applicants to show that an amide bond is not inherent in the peptide of Wade *et al.* when the MPEP makes it clear that "in relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Id.* In this case, the Examiner provides no extrinsic evidence supporting the statement that due to the "close proximity to one another and owing to their positive and negative charges, the amide bond be inherent to the peptide of Wade *et al.*" Accordingly, applicants request the Examiner provide such evidence or withdraw the grounds for rejection.

Additionally, applicants respectfully disagree that the peptide disclosed by Wade *et al.* would inherently contain an amide bond. As recognized by the skilled artisan, placing positively and negatively charged groups amino acid side chains in close proximity simply would not result in the formation of a covalent amide (peptide) bond because the energy required to form such a bond is too high. This is clear from the teachings in the art, exemplary of which is the statement that one

> function of the amino acid attachment (to a transfer RNA) is to activate the amino acid by generating a **high-energy** linkage at its carboxyl end so that it can react with the amino group of the next amino acid in the protein sequence to form a peptide bond. The activation process is **necessary** for protein synthesis because **nonactivated** amino acids **cannot** be added directly to a growing polypeptide chain. (In contrast, the reverse process, in which a peptide bond is hydrolyzed by the addition of water, is energetically favorable and can occur spontaneously.)

peptide bond

Alberts *et al.*, MOLECULAR BIOLOGY OF THE CELL, 3rd ed. (1994), at 228 (emphasis added; copy attached). Accordingly, in the absence of specific conditions, such as through the help of a tRNA, a high-energy amide bond cannot form. In fact, exactly the opposite will occur because amide bonds spontaneously break apart through hydrolysis by the addition of water.

Additionally, Wade *et al.* cannot anticipate claims 1, 7, 11, 36 and 39 because they fail to disclose every element of the claims. Specifically, Wade *et al.* fail to teach element (iii) of these claims, that "the amino acid sequence and/or at least one of the inter amino acid bonds of said analogue is not the same as that of the carboxy-

terminal sequence of naturally occurring mammalian growth hormone." The present claims are directed to analogues, i.e. modified forms, of growth hormone carboxy terminus, not naturally occurring forms of the growth hormone carboxy terminus. This directly contrasts to Wade *et al.* which only disclose synthetic copies of the naturally occurring form of the carboxy terminus, not analogues of the carboxy terminus.

Accordingly, applicants respectfully request the Examiner withdraw the rejection because the peptide of Wade *et al.* does not inherently contain an amide bond and Wade *et al.* fail to disclose every element of the claimed invention.

6. Claim Rejections — 35 USC §103

In the Office Action claims 1, 7, 11, 13, 16, 36, 37 and 39 were "rejected under 35 U.S.C. 103(a) as being unpatentable over Wade *et al.* in view of Ma *et al.* and Nicoll *et al.*"

As stated in the MPEP, "[t]o establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP § 2143.03. As discussed above, Wade *et al.* fail to teach or suggest all the elements of the independent claim 1. Specifically, Wade *et al.* fail to teach or suggest an analogue of the carboxy terminus of a mammalian growth hormone that has one or more features not found in a naturally occurring growth hormone. The same is true for both Ma *et al.* and Nicoll *et al.*, neither of which teaches or suggests an analogue of the carboxy terminus of a mammalian growth hormone that has at least one non-naturally occurring characteristic. As none of the references teach or suggest all of the claimed elements, the references fail to state a prima facie case of obviousness and applicants respectfully request the Examiner withdraw this rejection with regard to claims 1, 7-8, 11-12 and 36.

Additionally, "to establish a prima facie case of obviousness... it is essential that Office personnel find some motivation or suggestion to make the claimed invention in light of the prior art teachings." MPEP §2144.08 II.A (emphasis added). In the absence of a hindsight reconstruction, there is no suggestion or motivation to combine the references to achieve the claimed invention. As recognized by those skilled in the art, the

modification of a peptide to achieve functional activity is a complex matter because adding, deleting, substituting or otherwise modifying amino acids in a peptide sequence can greatly alter the properties and activity of the peptide.

Although Ma *et al.* teach that peptide fragments containing residues 176-191 or 177-191 of human growth hormone have certain activities, Ma *et al.* do not teach the desirability of using either one of these specific peptide fragments. Ma *et al.* simply build on previous research by testing to see whether lengthening the previously reported peptide containing residues 178-191 of human growth hormone activity by a few residues would have an effect on its activity. See, e.g., the column spanning pages 400 and 401. Ma *et al.* clearly state "both peptides [tested, hGH 176-191 and hGH 177-191,] contained the minimum active sequence (hGH 178-190), and were qualitatively and quantitatively **identical** in **all** biological activities tested." Ma *et al.* left column page 401 (emphasis added). In fact, in Ma *et al.*'s own words "it can be stated that peptides containing the minimum active sequence hGH 178-191 act directly on the target cells, and bring about inactivation of glycogen synthase and pyruvate dehydrogenase." Ma *et al.* page 409. Thus, one skilled in the art guided by the teachings of Ma *et al.* would focus their attention on the "minimally active sequence" and not be motivated to produce an analogue of residues 177-191 or 176-191 of hGH because Ma *et al.* clearly teach using these residues provide no specific advantage over using the shorter and more easily produced active sequence.

Nicoll *et al.* is cited for the proposition "that **many** amino acids may be substituted in growth hormone, including position 176 to tyrosine[.]" Emphasis added. In fact, Nicoll *et al.* teach that only 5 of these residues (31%) are conserved in the 16 residue sequence of human growth hormone including positions 176-191and another 4 or 5 for which there are "highly acceptable substitutions." Thus, there are numerous different possible combinations of substitutions that can be made based on the teachings of Nicoll *et al.* However, Nicoll *et al.* provide no teaching or suggestion that would motivate the skilled artisan to make only the substitution at residue 176 to the exclusion of the "many" other substitutions that can also be made. Moreover, Nicoll *et al.* do not teach any specific advantage that would be gained by substituting residue 176 or that

there is any particular relevance to residue 176. Selecting only the substitution at residue 176 also ignores the fact all of the other growth hormone sequences contain an identical additional amino acid between residues 183 and 184 not found in human growth hormone. Thus, one skilled in the art would have to pick only one very specific substitution out of many possible substitutions without any guidance or reasoning as to why that specific selection should be made.

In contrast, the present invention has, for the first time, provided a motivation to place a tyrosine at position 176 in an analogue of human growth hormone. Specifically, this elected species, SEQ ID NO:19, provides surprisingly superior results to naturally occurring human growth hormone fragment 177-191. In particular, the data set out in Tables 5-8 of the specification clearly show that SEQ ID NO:19 exhibits significantly greater inhibition of lipogenesis and enhancement of lipolysis than does the naturally occurring carboxy terminus of human growth hormone. For example, Table 5 indicates that SEQ ID NO:19 exhibits only 49% of control lipogenesis whereas naturally occurring human growth hormone exhibits upwards of 75% of control lipogenesis. Accordingly, SEQ ID NO:19 exhibits significantly greater inhibition of lipogenesis than the naturally occurring fragment. Similarly, when analyzed in terms of antilipogenesis of human abdominal adipose tissue (Table 6), SEQ ID NO:19 exhibits less than 50% of control lipogenesis whereas hGH 177-191 do not exhibit this degree of inhibition of lipogenesis. In terms of lipolytic activity, Tables 7 and 8 indicate that SEQ ID NO:19 induces a significantly greater level of lipolysis than naturally occurring hGH 177-191.

Accordingly, the determination that the particular modification of hGH which resulted in the development of SEQ ID NO:19 would correlate to unexpectedly superior anti-lipogenic and lipolytic potency is a completely surprising and unexpected outcome which would not be reasonably predicted. It is therefore respectfully submitted that in light of this surprising and superior anti-lipogenic and lipolytic potency, the elected species, SEQ ID NO:19, stands inventive over the prior art documents which neither disclose nor teach towards the nature of a modification which would lead to activities superior to that of the naturally occurring peptide. Therefore, applicants respectfully request the Examiner withdraw the obviousness rejections.

6. Conclusion

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

Date January 28, 2003 By _____

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MARKED UP VERSION SHOWING CHANGES MADE

In the claims:

1. (Twice amended) A peptide which comprises an analogue of the carboxyl-terminal sequence of a growth hormone, said carboxyl-terminal sequence containing amino acid residues 177-191 of human growth hormone:

Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe (SEQ ID NO: 1),

or a corresponding sequence of a non-human, mammalian growth hormone; wherein in said analogue

(i) amino acids at positions 182 and 189 of hGH are joined by a bond to promote a cyclic conformation; and**[/or]**

(ii) amino acids at positions 183 and 186 of hGH are joined by a salt bridge or a covalent bond**; and**

(iii) the amino acid sequence and/or at least one of the inter amino acid bonds of said analogue is not the same as that of the carboxy-terminal sequence of naturally occurring mammalian growth hormone

or an organic or inorganic acid addition salt thereof.

15. (Twice Amended) A peptide of the sequence:

Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-Y^2 (SEQ ID NO: 4),

wherein Y^2 is selected from the group of $CONH_2$ and alkyl amide groups;

a **[s]**cyclic disulfide thereof or an organic or inorganic acid addition salt thereof.

MOLECULAR BIOLOGY OF
THE CELL
THIRD EDITION

Bruce Alberts • Dennis Bray
Julian Lewis • Martin Raff • Keith Roberts
James D. Watson

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New York & London

quences into protein sequences. This is the essential "adaptor" function of the tRNA molecule: with one end attached to an amino acid and the other paired to a codon, the tRNA converts sequences of nucleotides into sequences of amino acids.

The second function of the amino acid attachment is to activate the amino acid by generating a high-energy linkage at its carboxyl end so that it can react with the amino group of the next amino acid in the protein sequence to form a *peptide bond.* The activation process is necessary for protein synthesis because nonactivated amino acids cannot be added directly to a growing polypeptide chain. (In contrast, the reverse process, in which a peptide bond is hydrolyzed by the addition of water, is energetically favorable and can occur spontaneously.)

The function of a tRNA molecule depends on its precisely folded three-dimensional structure. A few tRNAs have been crystallized and their complete structures determined by x-ray diffraction analyses. Both intramolecular complementary base-pairings and unusual base interactions are required to fold a tRNA molecule (see Figure 3–18). The nucleotide sequences of tRNA molecules from many types of organisms reveal that tRNAs can form the loops and base-paired stems of a "cloverleaf" structure (Figure 6–8), and all are thought to fold further to adopt the L-shaped conformation detected in crystallographic analyses. In the native structure the amino acid is attached to one end of the "L," while the anticodon is located at the other (Figure 6–9).

The nucleotides in a completed nucleic acid chain (like the amino acids in proteins) can be covalently modified to modulate the biological activity of the nucleic acid molecule. Such posttranscriptional modifications are especially common in tRNA molecules, which contain a variety of modified nucleotides (Figure 6–10). Some of the modified nucleotides affect the conformation and base-pairing of the anticodon and thereby facilitate the recognition of the appropriate mRNA codon by the tRNA molecule.

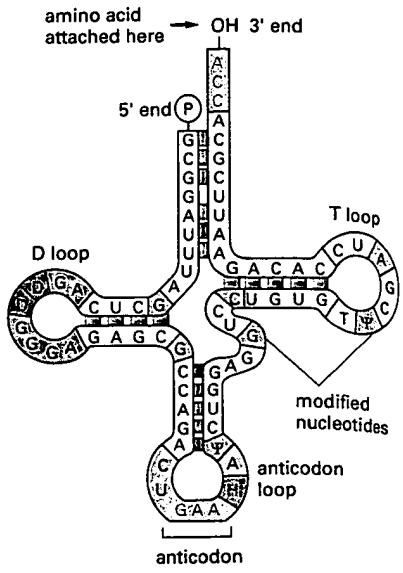

Figure 6–8 The "cloverleaf" structure of tRNA. This is a view of the molecule shown in Figure 6–9 after it has been partially unfolded. There are many different tRNA molecules, including at least one for each kind of amino acid. Although they differ in nucleotide sequence, they all have the three stem loops shown plus an amino acid-accepting arm. The particular tRNA molecule shown binds phenylalanine and is therefore denoted $tRNA^{Phe}$. In all tRNA molecules the amino acid is attached to the A residue of a CCA sequence at the 3′ end of the molecule. Complementary base-pairings are shown by *red bars.*

Specific Enzymes Couple Each Amino Acid to Its Appropriate tRNA Molecule [4]

Only the tRNA molecule, and not its attached amino acid, determines where the amino acid is added during protein synthesis. This was established by an ingenious experiment in which an amino acid (cysteine) was chemically converted into a different amino acid (alanine) after it was already attached to its specific tRNA. When such "hybrid" tRNA molecules were used for protein synthesis in a cell-free system, the wrong amino acid was inserted at every point in the protein chain where that tRNA was used. Thus the accuracy of protein synthesis is crucially dependent on the accuracy of the mechanism that normally links each activated amino acid specifically to its corresponding tRNA molecules.

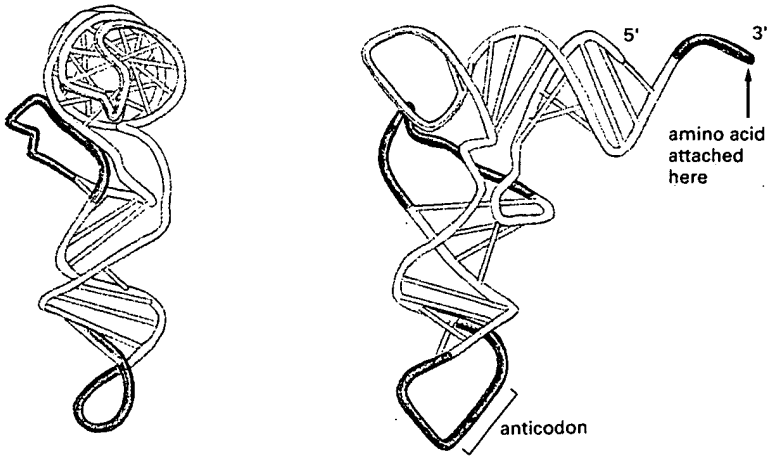

Figure 6–9 The folded structure of a typical tRNA molecule. Two views of the three-dimensional conformation determined by x-ray diffraction are shown. Note that the molecule is L-shaped; one end is designed to accept the amino acid, while the other end contains the three nucleotides of the anticodon. Each loop is colored to match Figure 6–8.